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New insights into epigenetic modifications in heart failure

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TABLE OF CONTENTS

1. ABSTRACT

Heart failure (HF) is a complex syndrome that occurs when the heart is unable to take in and/or eject sufficient blood to meet the needs. HF is generally accompanied by hypertrophic changes of cardiac myocytes, the hallmark of HF. At the molecular level, these changes in cardiomyocyte phenotypes are linked to reprogramming of gene expression. Therefore, understanding the molecular mechanisms involved in these gene expression changes in HF could allow for the development of new therapies for this pathology. One mechanism of gene expression regulation that attracts attention is epigenetic modifications, including DNA methylation, histone methylation and acetylation, microRNA, and long noncoding RNA. In this review, we will discuss diverse functions of these epigenetic modifications in HF, and highlight growing evidence for the important roles of epigenetic changes acting as biomarkers for early diagnosis and prognosis of HF, or even as therapeutic targets in HF.

2. INTRODUCTION

In the United States, more than 650,000 new cases of heart failure (HF) are diagnosed annually, and HF has become one of the largest contributors to disease burden and healthcare expenditure. Although there have been development of new diagnosis techniques and therapies for HF, the prognosis remains poor with a mortality rate of 50% within 5 years of diagnosis (1-3). HF is a complex syndrome that occurs when the heart is unable to take in and/or eject sufficient amounts of blood to meet the body's needs. Complex genetic predisposition

and multiple environmental factors contribute to HF; and it is the culmination of primary myocardial diseases, such as hypertension, myocardial ischemia, and coronary artery disease (3). Despite the diverse etiologies, HF is generally accompanied by hypertrophic changes of cardiac myocytes, which is the hallmark of HF (4). At the molecular level, these changes in cardiomyocyte phenotype are linked to reprogramming of gene expression. For example, during cardiac hypertrophy, fetal cardiac genes such as β-MyHC and ANF are reactivatied, while the genes such as α-MyHC and sarcoplasmic reticulum Ca^{2+} ATPase are downregulated (5).

Epigenetics refers to heritable changes in gene expression that do not involve changes in DNA sequence, but result from alterations related to packaging and/or posttranslational modifications (6). Epigenetic regulation occurs mainly by three key mechanisms: CpG island methylation mediated by DNA methyltransferases (DNMTs), histone modification including methylation and acetylation, and noncoding RNA (ncRNA) including microRNA (miRNA), long nocoding RNA (lncRNA) (6). A large range of functions have been attributed to epigenetic regulation, such as cell proliferation, apoptosis, cell invasion, and imprinting. This indicates that these molecules represent a major regulatory component of the eukaryotic genome. Not surprisingly, epigenetic modifications are emerging as important players in several human pathologies, including cardiovascular diseases (CVD) (7, 8). Although "cardiovascular epigenetics" is a relatively young research area, a considerable amount of data has already been accumulated, convincingly demonstrating the critical role of epigenetic mechanisms in HF (9, 10). This review provides an overview of recent discoveries that support an important role of current knowledge regarding the role of epigenetic regulation in HF.

3. EPIGENETIC MODIFICATIONS

3.1. DNA methylation

DNA methylation was the first epigenetic modification discovered in the mammalian genome, and constitutes the addition of a methyl group to the 5' carbon of the cytosine ring within CpG (cytosine preceding guanosine) dinucleotides.

Methylation of CpG sequences promotes gene silencing by acting as a docking site for methyl-binding proteins such as methyl-CpG binding protein 2 (MeCP2), which can oligomerize throughout the DNA and interact with a co-repressor complex to cause gene inactivation (11). The process of DNA methylation including de novo methylation and maintenance methylation, is catalyzed by DNMTs. DNMT3a and DNMT3b are responsible for de novo methylation, and DNMT1 is responsible for DNA methylation maintenance in somatic cells (11).

3.2. Histone modification

The nucleosome is the fundamental unit of chromatin, and encompasses about 146 base pairs (bp) of double-stranded DNA (dsDNA) wrapped around a histone octamer composed of two each of histones H2A, H2B, H3 and H4 (12). Histone proteins can undergo a variety of modifications such as acetylation, methylation and ubiquitination that occur on lysine (Lys) and arginine (Arg) residues on the N-terminal tails and at the core of histones. These different histone modifications create the histone code, which affects nuclear replication, chromatin assembly and transcription to regulate gene expression (13).

3.2.1. Histone acetylation

Histone acetylation is a dynamic process regulated by a balance of two families of enzymes: histone acetyltransferases (HATs) and histone deacetylases (HDACs). HAT enzymes act by acetylating specific Lys residues of the histone components (H2B, H3, and H4) of chromatin, while HDACs deacetylate these Lys residues (14).

The HATs currently include more than 20 members and are traditionally divided into two different classes. Type A HATs, such as Gcn5 and p300/CBP are located in the nucleus and act by acetylating nucleosome histones. Type B HATs, such as Hat1, are located in the cytoplasm and are responsible for the acetylation of newly synthesized histones before their assembly into nucleosomes (15). HDACs are divided into four distinct classes: Class I (HDAC1, 2, 3, and 8), class II (HDAC5, 6, 7, 9, and 10), and class IV (HDAC11) share similar sequences and show dependent on Zn dependent enzymatic activity; Class III (SIRT1, 2, 3, 4, 5, 6, 7) is a structurally unrelated NAD^+ dependent subfamily belonging to the Sirtuin family (16). Large numbers of studies have focused on the abilities of HATs and HDACs to acetylate and deacetylate histones and regulate chromatin. However, HDACs and HATs can also target non-histone proteins, and theseimportant posttranslational modifications regulate the function, stability, associated signaling and functions of these proteins and thereby affect a broad range of human disorders (17). The expression, location, targeted proteins and functions of these enzymes in different cells are complex and poorly understood.

HDAC and HAT inhibitors have emerged as novel therapies for several diseases (18). For example, two hydroxamic containing agents called SAHA and ITF 2357 have different effects on various zinc-dependent HDAC enzymes (e.g. class I and II HDACs), resulting in increased histone acetylation and gene transcription. Among them, SAHA was approved by the FDA for treatment of cutaneous T-cell lymphoma therapy (19).

3.2.2. Histone methylation

Histone methylation traditionally occurs at Lys and Arg residues of histone H3 (especially

Lys4/9/27/36/79, Arg2/17/26) and H4 (Lys20; Arg3). This includes mono-, di-, or trimethylation (20). In contrast to acetylation, which is correlated with transcriptional activation, histone methylation is involved in both activation and repression of transcription depending on which Lys and Arg residue is methylated and the degree of methylation. For example, trimethylation of histone H3 at Lys 9 (H3K9me3), H3K27me3, and H4K20me3 are related to gene repression, while H3K4me3, H3K36me3, and H3K79me3 are associated with transcriptional activation (20).

Similar to histone acetylation, histone methylation is a reversible process regulated by associated enzymes: histone methyltransferases (HMTs) and histone demethylases (HDMTs) (21). HMTs transfer one, two, or three methyl groups from S-adenosyl-L-methionine (SAM) to the Lys residue of histone. Three families of enzymes have been identified thus far that catalyz the addition of methyl groups donated from S-adenosylmethionine to histones (22). Two families of HDMTs have been recently identified that remove methyl groups from Lys residues. The majority of HDMTs contain either the Jumonji C (JmjC) domain (JmjC domain-containing histone demethylases, JHDM) or the Jumonji/ARID domain (Jumonji/ARID domain-containing proteins, JARID) (23).

3.3. NcRNA

The conventional view of gene regulation in biology has mostly focused on protein-coding genes via the central dogma: DNA → mRNA → protein. However, only approximately 1.5.% of the genome is responsible for protein coding and a large number of noncoding regulatory elements are transcribed into ncRNA, therefore ncRNAs constitute a large proportion of the total RNA. According to size, ncRNAs can be divided into two groups: small ncRNAs (<200 nucleotides, e.g. miRNAs and small interfering RNAs (siRNAs)) andlncRNAs (24). Among them, miRNAs and lncRNAs have become new stars in the exploration for their function in various physiological processes and several human pathologies (25-27).

3.3.1. miRNA

miRNAs currently refer to small RNAs about 19-25 nucleotides long, and are organized in the genome in monocistronic or polycistronic units located in the introns of host genes, in host exons, or in intergenic regions (28). miRNAs were first functionally identified in the *Caenorhabditis elegans* in the early 1990s (29). Since then, large numbers of miRNAs have been identified and investigated, and more than 1600 human miRNA sequences have been demonstrated to regulate a variety of biological processes, such as cell proliferation and differentiation (30).

Generally, miRNAs are transcribed by RNA polymerase II to generate primary miRNAs, which are then processed into pre-miRNAs by an enzyme complex composed of the RNase III endonuclease Drosha and the dsRNA binding protein Pasha. Pre-miRNAs are then transported to the cytoplasm from the nucleus by Ran-GTP and exportin-5, where they are further processed into mature miRNAs by the RNase III enzyme Dicer (28). The mature miRNAs interact with the protein Argonaute to form the RNA- inducing silencing complex. This complex binds to the 3' UTR of specific mRNA sequences, leading to negative regulation of protein synthesis or mRNA degradation (31). Because of this strong function in gene regulation, miRNAs have been shown to be involved in many different pathological processes such as cancer and CVD (25, 32).

3.3.2. LncRNA

The concept of functional lncRNAs was first introduced in 1992, following the identification of the X-inactive specific transcript (XIST), which is responsible for X-chromosome inactivation (33). In the past two decades, thousands of lncRNAs have been identified, although the majority of them still have not been functionally characterized. LncRNAs are currently defined as RNA transcripts that are longer than 200 nucleotides, often polyadenylated and devoid of evident open reading frames, and with unknown protein-coding function (34). lncRNAs can be polyadenylated or not, nuclear or cytoplasmic, and appear less conserved than protein-coding RNAs. According to the relative position in transcriptome, lncRNAs can be classified into the following five categories: sense, antisense, bidirectional, intronic, and intergenic (35).

Accumulating studies have demonstrated that lncRNAs participate in various physiological processes such as cellular differentiation, and many diverse diseases including cancer and CVD (27, 36, 37). Almost every stepof gene regulation can be regulated by lncRNAs, including chromosome dosage-compensation, imprinting, transcription, nuclear and cytoplasmic trafficking, epigenetic regulation, etc. (38). However, the precise mechanism of how lncRNAs function still remains unclear and is under extensive investigation. Wang and Chang summarized the known archetypes of molecular functions of lncRNAs as signals, decoys, guides, and scaffolds (26):

3.3.2.1. Signals

As signals, lncRNAs show cell type and time-specific expression and respond to stimuli. For instance, the lncRNA Frigidair has an anterior pattern of expression, while HOTAIR is expressed in cells with distal and posterior positional identities (39). Huarte *et al.* demonstrated that the lncRNA called lincRNA-p21serves as a repressor in p53-dependent transcriptional responses and plays a role in triggering apoptosis (40).

3.3.2.2. Decoys

Acting as molecular decoys, lncRNAs can bind and titrate away proteins or RNA targets to negatively

regulate the expression of their targets. For example, the lncRNA PANDA can directly bind to and sequestrate NF-YA, resulting in inhibition of apoptotic genes and promotion of cell survival (41).

3.3.2.3. Guides

The third archetype of lncRNAs, the guide, refers to RNAs that bind proteins, then direct localization of the ribonucleoprotein complex to specific targets to change gene expression. These lncRNAs can guide changes in gene expression either *in cis* (e.g. Air, and HOTTIP) or in trans (e.g. HOTAIR, LincRNA-p21). For example, the lncRNA HOTAIR recruits the Polycomb Repressive Complex 2 (PRC2) to specific target genes, leading to H3K27me3 and epigenetic silencing of metastasis suppressor genes (42).

3.3.2.4. Scaffolds

lncRNAs acting as scaffolds serve as adaptors to bind relevant molecular components to regulate gene expression, which may be the most functionally complex class depending on the different binding domains of the lncRNA. For instance, the antisense lncRNA ANRIL serves as a molecular scaffold. ANRIL combines PRC1 and PRC2, recruiting multiple sets of chromatin-modifying complexes to the target gene for silencing (43, 44).

4. DNA METHYLATION IN HF

Generally, DNA methylation is thought to contribute mainly to gene silencing by preventingthe accessibility of DNA binding elements present in the promoter of genes, which play essential roles in embryonic developmentand genomic imprinting (11, 45). DNA methylation has been shown to be linked to biological processes of various diseases including cancer and CVD (46-48). Studies of the function of DNA methylation in HF were recently started.

Considering DNA methylation in HF, a series of genome-wide studies recently suggested a role for DNA methylation in cardiomyopathies (49-51). For example, Mehregan *et al.* compared DNA methylation between the hearts of end-stage cardiomyopathic patients and normal human. They showed that upregulated genesare associated with reduced methylation in their promoters, while downregulated genes in cardiomyopathy were independent of changes in gene promoter methylation (49). In addition, Movassagh *et al.* identified three angiogenic factors whose expression could be regulated by DNA methylation in human HF: platelet/ endothelial cell adhesion molecule 1, angiomotin-like 2, and Rho GTPase activating protein 24 (52). Hass *et al.* detected methylation differences in pathways related to HF in the myocardia of patients with idiopathic dilated cardiomyopathy (DCM) and found aberrant DNA methylation was associated with significant changes in LY75 and ADORA2A mRNA expression, which have been demonstrated important for adaptive or maladaptive pathways in HF (53).

In accordance with the role of DNA methylation in cardiomyopathies, attention has been paid to DNMTs in HF. It was found that TNF-α could directly enhance cardiac SERCA2a methylation by upregulating DNMT1 (54). Hydralazine modulated calcium homeostasis in cardiomyocytesin isoproterenol-induced HF rats. Mechanistically, hydralazine induced the decline of DNMT1, which led to down-regulation of SERCA2apromoter methylation and increased SERCA2a expression (55). Generating mice with cardiomyocyte-specific deletion of *Dnmt3a* and *Dnmt3b* responsible for *de novo* CpG methylation, Thomas *et al.* found that cardiac myocyte DNMT3a/3b are dispensable for cardiac function and remodeling after chronic pressure overload in mice (56). However, Tao *et al.* showed that DNMT3a may silence RASSF1A to upregulate ERK1/2 in rat cardiac fibrosis (57). Additionally, Vujic *et al.* reported that DNMT3b was the predominant DNMT in the adult heart, and cardiac specific deletion of *Dnmt3b* led to an accelerated progression to severe systolic insufficiency and myocardial thinning without a preceding hypertrophic response, accompanied by widespread myocardial interstitial fibrosis and myosarcomeric disarray (58). Although it is controversial which DNMT is at work in HF, inhibition of DNA methylation by the inhibitor 5-aza-2′-deoxycytidine has been tested in animal models of HF (59-61), indicating a novel treatment strategy for HF.

5. HISTONE MODIFICATION IN HF

5.1. Histone acetylation

Most research related to histone acetylation in HF has focused on HDACs and HATs and is summarized in Figure 1. Studies in animal models demonstrated that class II HDACs, such as HDAC5, HDAC9 and HDAC4, have anti-hypertrophic activity.HDAC5 and HDAC9 knockout mice were sensitive for pro-hypertrophy stimuli to development of cardiac hypertrophy and HF. This was dependent on their ability to bind to and inhibit Mef2c, a transcriptional factor that promotes gene expression of pro-hypertrophy genes (62-64). Similarily, HDAC4 knockout mice showed cardiac hypertrophy (65, 66).

In contrast to class II HDACs, class I HDAC2demonstrated a role in pro-hypertrophy. *Hdac2* deficiency attenuated cardiac hypertrophy in hearts exposed to pro-hypertrophy stimulation; in contrast, mice overexpressing HDAC2 are over-sensitive to these stimuli. This pro-hypertrophy activity was associated with its ability to repress the expression of Inpp5f, which encodes PIP3 phosphatase, a negative regulator of the pro-hypertrophy PI3K–Akt– Gsk3b pathway (67). Similar to HDAC2, the function of the class III HDAC family was recently studied in HF and has also been shown to

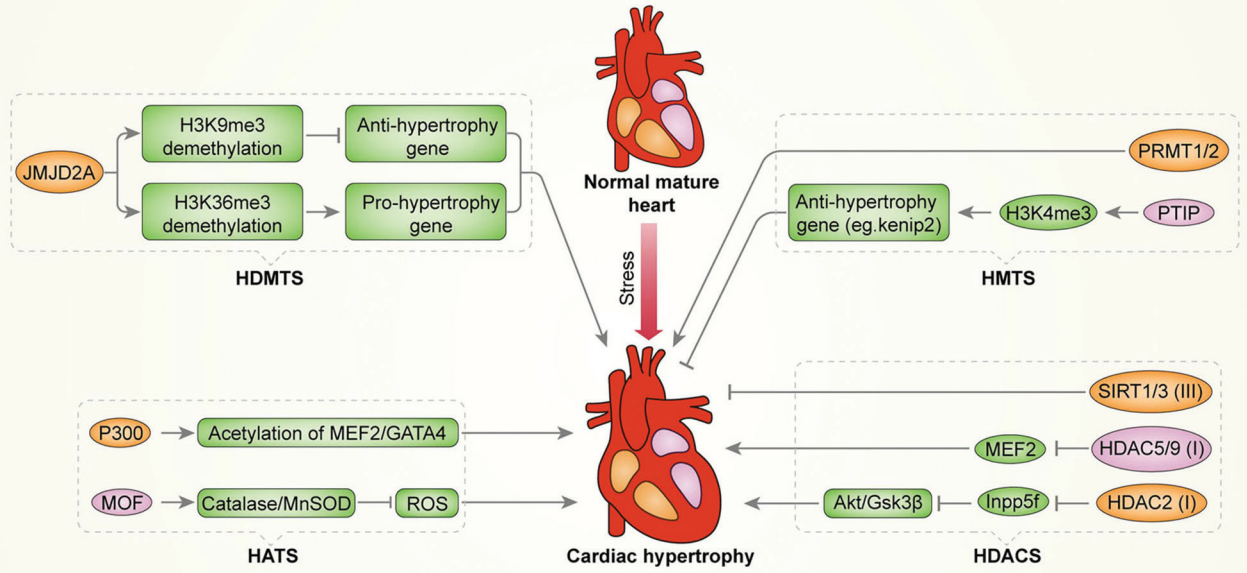

Figure 1. Model of histone modifications in HF. During the process of cardiachypertrophy, two epigenetic enzymes (PRMT1/2) become upregulated and an HDMT, JMJD2A, demethylates H3K9me3 and H3K36me3 to promote hypertrophic response to TAC.A key component of the H3K4me complex, PTIP, increases H3K4me3 to promote anti-hypertrophic genes (e.g. Kcnip2) and protect the heart. In response to cardiac stress stimuli, p300 acetylatesnon-histone proteins such as GATA-4 and MEF2 and act as HATs to promote hypertrophy, while another HAT called MOF accelerateshypertrophy by inhibiting the reactive oxygen species (ROS) response. Among HDACs, HDAC5/9bind to and inhibit Mef2c (promoting pro-hypertrophygenes) to inhibit hypertrophy, and two sirtuins (SIRT1 and SIRT3, belonging to HDAC III) play protective roles in failing hearts whereas HDAC2 (a class I HDAC) represses the expression of Inpp5f (a negative regulator of the pro-hypertrophy PI3K–Akt– Gsk3b pathway) to promote hypertrophy.

exhibit pro-hypertrophy function. For instance, emerging evidence indicates that two sirtuins (SIRT1 and SIRT3) play protective roles in failing hearts (68, 69).

While HDACs played dual roles in hypertrophy, current evidence revealed that HATs such as p300 act as pro-hypertrophic factors. p300 and the related CBP are transcriptional co-activators that are involved in a variety of cellular signaling and gene regulation during development (70). Gusterson *et al.* first demonstrated that p300 and CBP play an essential role in cardiac hypertrophy depending on their HAT activity: inhibition of either CBP or p300 inhibited phenylephrine- induced hypertrophy, while overexpression of these co-activators could induce hypertrophic growth of cardiomyocytes (71). Additionally, p300 can also acetylate certain non-histone proteins, such as transcriptional activators and coactivators (17). Several studies found that, in the p300 regulation of hypertrophy, p300 can directly acetylate non-histone proteins such as GATA-4 (72-74) and hypertrophy-responsive transcriptional factors like MEF2 (75).

In contrast to the pro-hypertrophic function of p300, Qiao *et al.* first identified a novel anti-hypertrophic HAT MOF, which belongs to the MYST family. MOF expression was down-regulated in failing human hearts and hypertrophic murine hearts. Cardiac-specific MOF overexpression protected mice fromtransverse aortic constriction (TAC)-induced cardiac hypertrophy. Mechanistically, MOF overexpression increased the expression of catalase and MnSOD, which blocked TAC-induced ROS and ROS downstream c-Raf-MEK-ERK pathway that promotes hypertrophy (76).

5.2. Histone methylation

While the role of histone acetylation in HF has been largely investigated, histone methylation remains poorly studied in this pathology. Keneda and colleagues found that epigenetic marksH3K4me3 and H3K9me3 are altered in HFin rats and human (77). During cardiac hypertrophy, downregulation of the cardiomyocyte gene desmin and b-MyHC was correlated with an increase in H3K9me3 (78), and the increased expression of Nppb and Nppa genes was correlated with increased dimethylation of H3K4 (79).

Because histone methylation marks were altered in both human and animal samples, the potential roles for HMTs and HDMs in HF were further explored (data summarized in Figure 1). Recent studies demonstrated that two epigenetic enzymes, protein arginine methyltransferase type 1 and type 2 (PRMT1 and PRMT2), involved in methylation of Arg residues and are overexpressed in patients with three-vessel coronary disease (80). Using an inducible system to ablate a key component of the H3K4me complex in cardiac cells,PAX interacting protein 1 (PTIP), in a mouse model revealed that reduction of H3K4me3 in differentiated cardiomyocytes was sufficient to alter gene expression profiles such as Kv

Table 1. Dysregulation of lncRNAs in HF

lncRNA	Expression	Function and potential mechanism	HF	Reference
Fendrr	Unknown	Essential for the development oflateral plate mesoderm; binds to the PRC2 complex to regulate the expression of GATA-6, NKX2-5, FOXF1, TBX3, IRX3, and PITX2 genes	No description	110
Bvht	Unknown	Required for cardiomyocyte differentiation and maintaining the cardiac phenotype in neonatal cardiomyocytes; interacts with SUZ12 (a component of PRC2) to regulate gene expression	No description	111
MIAT	Upregulated	Six SNPs in MIAT in myocardial infarction; unknown mechanism	Myocardial infarction	112
Kcnq1ot1	No description	Regulates the expression of the potassium channel KCNQ1	No description	114
Mhrt	Downregulated	Prevents Brg1 from recognizing its genomic DNA targets, thus inhibiting chromatin targeting and gene regulation by Brg1	Cardiac hypertrophy	115
CHRF	Upregulated	Downregulates miR-489 expression to regulate Myd88 expression	Cardiac hypertrophy	116
APF	Upregulated	Regulates miR-188-3p to suppress ATG7 expression and autophagic cell death	Myocardial infarction	117
LIPCAR	Downregulated early, but upregulated during later stages	A novel biomarker of cardiac remodeling and predicting future death in HF patients; unknown mechanism	Myocardial infarction	131

channel-interacting protein 2 (Kcnip2), which regulates a cardiac repolarization current downregulated in HF (81). H3K4me3 is required to maintain the transcription program in adult cardiomyocytes and could be involved in regulating gene expression changes in HF (81). Zhang's report showed that JMJD2A/KMD4, a HDMT belonging to the JHDM family and responsible for the demethylation of H3K9me3 and H3K36me3, was involved in cardiac hypertrophy (82). JMJD2A expression was upregulated in human hypertrophic patients. Inactivation of *Jmjd2a* resulted in an attenuated hypertrophic response to TAC-induced pressure overload, whereas Jmjd2a-Tg mice displayed exacerbated cardiac hypertrophy. Mechanistically, four-and-a-half LIM domains 1 (FHL1), a key component of the mechanotransducer machinery in the heart, was identified as a direct target of JMJD2A. JMJD2A interacted synergistically with SRF and myocardin, bound to the FHL1 promoter to upregulateFHL1 expression and downregulated H3K9 trimethylationin response to TAC (82). Together, these experiments indicated a potential modulator function for histone methylation in HF.

More recently, Bruneau and colleagues demonstrated that the alteration of epigenetic markers, including H3K27ac, H3K4me1, H3K4me3, and H3K27me3, were involved in gene expression regulation during cardiomyocyte differentiation. This suggests a potential role for histone methylation in the molecular etiology of congenital heart disease (83). However, the role of HMTs and HDMs such as EZH2 and JMJD3 in HF, which are responsible for H3K27me3, require further investigation.

6. NCRNA: MIRNAS AND LNCRNAS ARE KEY REGULATORS OF HF

6.1. microRNA

Since Rooij *et al.* first identified the function of miR-195 in HF (84), many miRNAs have been shown to be dysregulated in the failing heart and play critical roles in the pathogenesis and progression of HF (Table 1).

Mir-1 was first discovered as a muscle-specific miRNA in mice (85), and accounted for about 40% of all miRNA transcripts in the mouse heart (86). Sayed *et al.* first demonstrated the downregulation of miR-1 in TAC-induced cardiac hypertrophy (87). Karakikes *et al.* recently showed that adenoviral delivery of miR-1 to TAC-treated mice was able to reverse hypertrophy and ventricular dysfunction–associated TAC (88). Then, multiple groups further identified several genes known to be involved in cardiac hypertrophy as downstream targets of miR-1 (87-91). These included MEF2a, GATA4, insulin-like growth factor-1, NFAT, NCX1 and twinfillin. Furthermore, another two muscle-specific miRNAs, miR-133 (92-94) and miR-378 (95-97), were also found downregulated in the failing heart and play critical roles in HF.

Conversely, a series of up-regulated miRNAs (miR195, miR-499, miR-23, miR-24, miR199, etc.) have been shown to participate in HF. For example, miR-195 was the first identified miRNA regulating the progression of cardiac hypertrophy. Overexpression of miR-195 in cardiac cells *in vivo* was shown to drive cardiac hypertrophy, which rapidly transitions to HF (84). Mechanistically, miR-195 promoted

hypertrophy by targeting several genes involved in multiple signaling pathways such as HMGA, MO25 involved in apoptosis (98, 99). MiR-499 was also recently shown to be up-regulated in hypertrophic and ischemic cardiomyopathy (100, 101).miR-499 was sufficient to cause murine HF and accelerated the maladaptation to pressure overloading in mice and humans (100, 101), by regulating WNT, JAK/STAT, and apoptosis signaling pathways during the development of hypertrophy. MiR-208a is a cardiac-specific miRNA embedded within an intron of the α-MHC gene (102). Overexpression of miR-208a led to up-regulation of β-MHC in mice and was sufficient to induce arrhythmia, fibrosis, and hypertrophic growth in mice and poor clinical outcomes in humans with DCM (103-105). Martins *et al.* recently described that miR-199b was elevated in mouse models with pathological hypertrophy and in human failing hearts. MiR-199b modulated Dyrk1a, constituting a feed forward mechanism that enhanced pathological cardiomyocyte hypertrophy processes (106). While these miRNAs were mainly identified in cardiomyocytes, cardiac fibroblasts secrete exosomes enriched with miR-21 during stress, which can be transportedto cardiomyocytes and inhibit the expression of anti-hypertrophic proteins SORBS2 and PDLIM5, leading to cardiomyocytes hypertrophy (107).

In contrast to the above miRNAs, the function of miR-25 in HF is more complex. Using high-throughput functional screening of the human microRNAome, Wahlquist *et al.* showed that miR-25 potently delayed calcium uptake kinetics in cardiomyocytes and was upregulated in HF both in mice and humans. They demonstratedthat inhibition of miR-25 blocked and reversed the disease in mice partly by increasing the mRNA of SERCA2a (108). In contrast, Dirkx *et al.* demonstrated that miR-25decreased acutely after aortic constriction in mice, and inhibition of miR-25evoked spontaneous cardiac dysfunction and sensitized the murine myocardium to HF in a Hand2-dependent manner (109). These two seemingly contradictory studies reflect that mi-R25 may play different roles in different stages of HF pathogenesis.

6.2. LncRNA

Although the role of miRNAs is being largely investigated in cardiovascular biology and HF, study of lncRNA in this field is only beginning to emerge and is summarized in Table 1.

Two recent studies demonstrated that two lncRNAs, *Fendrr* and Braveheart (*Bvht*), were involved in the development of lateral mesoderm in the heart and differentiation of cardiomyocytes, respectively,both by acting as modulators of chromatin signatures that define gene activity (110, 111). Phillip *et al.* showed that *Fendrr* was specifically expressed in the nascent lateral plate mesoderm and essential for proper heart and body wall development in the mouse. Loss of *Fendrr* in mice caused embryonic lethality around E13.5. due to impaired heart function. The heart of these mice presented with cardiac hypoplasia leading to the thickness of the ventricular walls, which was linked to abnormal proliferation of cardiac myocytes. Mechanistically, *Fendrr* bound to the PRC2 complex, which downregulated several transcription factors (e.g. GATA-6, NKX2-5, FOXF1) controlling lateral plate or cardiac mesoderm differentiation (along with decreased H3K27me3 and/or an increase in H3K4me3 at the promoters of genes) (110). Klattenhoff *et al.* identified that the lncRNA *Byht* was essential for progression of nascent mesoderm toward a cardiac fate. *Byht* was required for cardiomyocyte differentiation and for maintaining the cardiac phenotype in neonatal cardiomyocytes by regulating expression of core gene regulatory networks involved in defining cardiovascular cell fate, such as mesoderm posterior (MesP1). Similar to *Fendrr* regulation for cardiomyocyte differentiation, *Bvht* modulated the epigenetic profile of cells through interaction with SUZ12, a component of PRC2 (111). However, the roles of *Fendrr* and *Bvht* in HF and other CVD haven't been described.

Aside from the role of lncRNA in heart development, functions of these molecules in HF have also been explored. Through a large-scale case-control association study, Nobuaki *et al.* identified a novel lncRNA myocardial infarction associated transcript (MIAT) and revealed six SNPs in MIAT associated with myocardial infarction (112). Another study by Lee *et al.* discovered 15 lncRNAs that modulated mouse hearts after pressure-overload-induced by transaortic constriction, indicating the involvement of lncRNAs in HF (113). Correct potassium channel activity is required for normal cardiac functioning, and Korostowski *et al.* showed that alteration of the Kcnq1ot1-mediated control of Kcnq1 (encoding a potassium channel) could be responsible for abnormal heart function (114). Mechanisms of these lncRNAs in HF are still unclear.

More recently, a cardiac-specific lncRNA named myosin heavy-chain-associated RNA transcripts (Myheart, or Mhrt) was identified in adult hearts of mice. During pathological stress induced hypertrophy, Mhrt expression is inhibited, and restoring Mhrt to the pre-stress level can protect the heart from hypertrophy and failure. Mechanistically, the activated Brg1-Hdac-Parp chromatin repressor complexcaused downregulation of Mhrt, while Mhrt prevented Brg1 from recognizing its genomic DNA targets, thus inhibiting chromatin targeting and gene regulation by Brg1, indicating the crucial role of Mhrt–Brg1 feedback circuit for heart function (115).

Furthermore, two studies by Wang *et al.* demonstrated that two lncRNAs regulated HF by targeting miRNAs. They identified the lncRNA cardiac hypertrophy related factor (CHRF) from hypertrophic cardiomyocytes and showed that CHRF promote angiotensin II-induced

cardiac hypertrophy by downregulating miR-489 expression to regulate Myd88 expression (116). They also identified the lncRNA autophagy promoting factor (APF), which regulates miR-188-3p and thus affects ATG7 expression, autophagic cell death and myocardial infarction (117).

7. CLINICAL APPLICATIONS OF EPIGENETIC MODIFICATIONS IN HF

7.1. HF diagnosis and prognosis

miRNAs can be detected in bodily fluids such as urine, saliva, and plasma, and extracellular miRNAs are stable and resistant to freeze/thaw cycles. This makes them attractive candidates for disease biomarkers, suggesting that cell-free circulating miRNA may be promising biomarkers for human diseases diagnosis (118, 119).

Indeed, there have been several investigations of the use of miRNAs as instruments in HF diagnosis. For example, one study showed that seven miRNAs (miR-103, miR-142-3p, miR-199a-3p, miR-23a, miR-27b, miR-324-5p, and miR-342- 3p) could be used to distinguish between HF, exacerbated chronic obstructive pulmonary disease, other causes of dyspnea, and healthy controls (120). Matsumoto *et al.* screened microRNAs in 21 patients who experienced development of HF within 1 year after one AMI,and demonstrated that three circulating p53-responsive miRNAs (miR-192, miR-194 and miR-34a) are predictive indicators of heart failure after acute myocardial infarction (121). A large number of additional explorations for the application of circulating miRNAs have been published (122-127).

In addition to the use of circulating miRNAs for HF diagnosis, recent studies have shown that circulating miRNAs may also be used for HF prognosis. In the hypertensive rat model, circulating levels of miR-16, miR-20b, miR-93, miR-106b, miR-223, and miR-423-5p were significantly increased in response to hypertension-induced HF. This effect was blunted after treatment with an angiotensin-converting enzyme inhibitor, indicating that plasma miRNAs can be used as indicators of disease progression or therapeutic efficacy in HF (128). Marfella *et al.* analyzed plasma miRNAs in 81 HF patients treated with cardiac resynchronization therapy. The responders to this therapy showed higher expression of five miRNAs compared to non-responders (miRNA-26b-5p, miRNA-145-5p, miRNA-92a-3p, miRNA-30e-5p, and miRNA-29a-3p) (129).

Similar to miRNA, lncRNAs can be stable and detected in the peripheral blood of patients, suggesting that circulating lncRNAs in plasma can be promising biomarkers for disease diagnosis (130). Global transcriptomic analyses of plasma RNA from patients with or withoutleft ventricular remodeling after myocardial infarction showed that the mitochondrial long noncoding RNA uc022bqs.1 (LIPCAR) was downregulated early after myocardial infarction but upregulated during later stages (131). LIPCAR levels identified patients that developed cardiac remodeling andthe results were independent of other risk markers associated with future cardiovascular deaths, indicating a novel biomarker of cardiac remodeling and predicting future death in HF patients (131).

7.2. HF therapy

Considering the important roles of DNA methylation, histone acetylation and methylation in HF, inhibitors targeting DNMTs, HATs, HDACs, HMTs and HDMTs may provide novel treatment strategies for HF. Indeed, inhibition of DNA methylation by its inhibitor 5-aza-2′-deoxycytidine in the mouse model has been shown to alleviate rat cardiac hypertrophy (59-61). Curcumin, a polyphenol responsible for the yellow color of the spice turmeric, possesses HAT inhibitory activity with specificity for the p300/CREB-binding protein. The effect of curcuminon the pro-hypertrophic function of p300 was examined *in vivo* in four different heart failure models: hypertensive heart disease in salt-sensitive Dahl rats and surgically induced myocardial infarction in rats, and mouse cardiac hypertrophy induced by aortic banding and PE infusion. In all models, curcumin suppressed cardiac hypertrophy through the disruption of p300-HAT–dependent transcriptional activation (histone acetylation, GATA4 acetylation, and DNA-binding activity), indicating that the nontoxic dietary compound curcumin could be a novel therapeutic strategy for HF in humans (132-134). Although different kinds of HDACshave different, complex roles in HF, HDAC inhibitors have been suggested to restore the dysregulated gene expression in hypertrophied cardiac cells, as a treatment for HF. Studies showed that cardiac fibrosis and hypertrophy can be prevented bytreatment with inhibitors of class I HDACs (e. g. MPT0E014, Mocetinostat) in animal models (135-137). Additionally,the HDACI and II inhibitor trichostatin-A (TSA)can attenuate pathological cardiac remodeling in a serious of mouse models suchas isoprotenol-, angiotensin II- and pressure overload-induced hypertrophy (138-140).

Currently, miRNA-based therapies (antimiRs and miRNA mimics (miR-mimics)) for disease have attracted a lot of attention. In the HF field, Thum *et al.* used a locked nucleic acid (LNA) miR-21 inhibitor to show that inhibition of miR-21 significantly reversed the progression of cardiac hypertrophy and fibrosis and attenuated the impairment of cardiac function (141). Martins *et al.* showed that administration of a specific antagomir for miR-199b to mice after transverse aortic constriction could cause marked inhibition and reversal of hypertrophy and fibrosis in mouse models of HF (106). Montgomery's study clarified that the therapeutic inhibition of miR-208a by subcutaneous

delivery of antimiR-208a prevented pathological myosin switching and cardiac remodeling, and further improved cardiac function, overall health, and survival (104). The application of miR-mimics for HF therapy is supported by a recent study demonstrating that the adenoviral delivery of miR-1 to TAC-treated mice was able to reverse hypertrophy with improvement in fractional shortening, reversal of ventricular dilatation, and decreased fibrosis (88). Studies have also shown that increased expression of endogenous miRNAs such as miR-133 are cardio-protective during HF and suggested that it might be targeted therapeutically to restore cardiac function by miR-mimics (142). Similar to miRNA, lncRNA-based therapies have recently been under explored in kinds of human diseases including cancer, these therapies for HF need further investigations.

8. CONCLUSIONS

In this review, we summarized a series of evidence implicating epigenetic modification as an important regulatory mechanism for the cardiovascular system. We mainly focused on a subset of epigenetic modifications in HF: DNA methylation, histone acetylation/methylation and ncRNA (miRNAs and lncRNAs), which mediate multiple aspects of HF, from specific gene expression to responses to disadvantageous environmental stimuli.

According to these data, understanding the role of epigenetic mechanisms in cardiac hypertrophy and failure may provide a basis for the development of HF diagnosis, prognosis and therapy. A new therapeutic approach to HF could take advantage of specific inhibitors of epigenetic enzymes; appropriate intervention of ncRNAs could correct dysregulated gene expression of these cells. And thanks to the detection of circulating ncRNAs, the novel ncRNA-based diagnosis approach to HF is developing.

However, future questions and challenges in the field of “cardiovascular epigenetics” are associated with the multiplicity and complexity of these regulatory mechanisms (10, 143). For example, the current investigations of epigenetic mechanisms in HF are mainly focused on cardiomyocytes, while these mechanisms in cardiac fibroblasts and endothelial cells during these processes are still unclear. The combinational biological functions of various epigenetic modifications in HF also require further investigation. In addition, several clinical studies and *in vivo* animal studies have already implicated some candidate ncRNAs (miRNAs and lncRNAs) associated with clinical characteristics in HF and ncRNA intervention as novel therapies in HF. However, considerable limitations are present in clinical applications including diagnosis, prognosis and treatment. Firstly, the stability of circulating ncRNAs remains largely unknown, and the levels of ncRNA transcripts are variable and difficult to detect during different disease stages. Secondly, it is still difficult to determine the origins of circulating ncRNAs that have been detected in HF patients (144). Thirdly, several common challenges in RNA therapeutics, such as lack of reliable delivery methods and optimal dosage regimes, limited effective vector types, have become obstacles for the success of ncRNA-based therapy (144, 145). All these lead to limitations for the clinical application of ncRNAs for HF diagnosis, prognosis and treatment.

At present there are many challenges for the potential application of epigenetic modifications in HF diagnosis, prognosis, and treatment. Even so, epigenetics-based research will undoubtedly fuel an exciting new frontier, promoting investigations for ideal biomarkers and therapeutic targets for HF in the near future.

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Abbreviations: HF: heart failure; DNMTs: DNA methyltransferases; ncRNA: noncoding RNA;miRNA: microRNA;lncRNA: long nocoding RNA; CVD: cardiovascular diseases; CpG: cytosine preceding guanosine; MeCP2: methyl-CpG binding protein 2; bp: base pairs; dsDNA:

double-stranded DNA;Lys: lysine; Arg: arginine; HATs: histone acetyltransferases; HDACs: histone deacetylases; H3K9me3: histone H3 at Lys 9; HMTs: histone methyltransferases; HDMTs: histone demethylases; JHDM: JmjC domain-containing histone demethylases; JARID: Jumonji/ARID domain-containing proteins; siRNAs: small interfering RNAs;XIST: X-inactive specific transcript; PRC2: Polycomb Repressive Complex 2; DCM: dilated cardiomyopathy; PE: phenylephrine; TAC: transverse aortic constriction; PRMT1 and PRMT2: protein arginine methyltransferase type 1 and type 2; PTIP: PAX interacting protein 1; FHL1: four-and-a-half LIM domains 1; *Bvht*: Braveheart; MesP1: mesoderm posterior; MIAT: myocardial infarction associated transcript; Mhrt: myosin heavy-chain-associated RNA transcripts, Myheart; CHRF: cardiac hypertrophy related factor; APF: autophagy promoting factor; TSA: trichostatin-A

Key Words: Heart Failure, Cardiac Hypertrophy, DNA Methylation, Histone Methylation, Histone Acetylation, miRNA, lncRNA, Review

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